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BUNNER, BRIDGET E

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,837	LU ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears in the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 February 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 7,18-31 and 33-39 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-6,8-17 and 32 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) 1-39 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 13 October 2000 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____ .
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) Other: _____

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 09 April 2002 (Paper No. 9) has been entered in full.

Election/Restrictions

Applicant's election with traverse of Group A, claims 1-6, 8-17, and 32, drawn to an isolated CLASP-2 polynucleotide, an expression vector, a host cell system, and a method of producing a CLASP-2 polypeptide in Paper No. 13 (23 August 2002) is acknowledged. The traversal is on the ground(s) that Groups A, F, and G should be rejoined. This is not found persuasive because, as discussed in the Office Action of 17 June 2002 (Paper No. 11), the polynucleotide of Invention A can be used in materially different processes other than the methods of Groups F and G, such as DNA purification and gene therapy (MPEP § 086.05(h)). Each of groups A, F, and G are unique invention, requiring a unique search of the prior art. Searching all of the inventions in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

Applicant's election with traverse of the nucleic acid sequence of SEQ ID NO: 1 in Paper No. 13 (23 August 2002) and the amino acid sequence of SEQ ID NO: 2 in Paper No. 17 (10 December 2002) is acknowledged. The traversal is on the ground(s) that SEQ ID NOs: 1, 3, 5, 9 cover isoforms of human CLASP-2 cDNA and that SEQ ID NOs: 2, 4, 6, 10 cover multiple forms of human CLASP-2 polypeptides produced by alternative exon usage. This is not found persuasive because each polynucleotide and polypeptide sequence is a unique sequence requiring a unique search of the prior art. Searching all of the sequences in the instant application would

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provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches. Additionally, since each of the polynucleotide and polypeptide sequences are different from one another, each may have diverse structural and functional features. Certain positions in the sequence are critical to the polypeptide's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. It is noted that Applicant's arguments directed towards the restriction requirement of a PDZ domain species has been found persuasive and the species have been rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7, 18-31, and 33-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14 (04 September 2002).

It is noted to Applicant that although claims 30 and 31 may recite unintentional errors, Applicant must comply with 37 CFR 1.121 to make claim amendments.

Claims 1-6, 8-17, and 32 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 14 May 2001 (Paper No. 6) was considered by the examiner.

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (Paper No. 9, 09 April 2002) has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (Paper No. 14, 03 December 2001) are withdrawn.

Specification

1. The disclosure is objected to because of the following informalities:
 - 1a. Patent applications are referenced throughout the disclosure (pg 2, line 10; pg 35, line 23). The status of the applications must be updated.
 - 1b. At page 117, line 5, it is not clear of the meaning of the following sentence: "(Please provide some specific regions.)"
 - 1c. The specification at page 118, line 7 contains a reference to a specific product catalog number, which is subject to change over time. (Note, this issue could be overcome by adding the complete catalog information, such as year and volume or by deleting the catalog number.)
 - 1d. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See page 15, lines 19). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
 - 1e. The Brief Description of Drawings at pg 10 of the specification does not refer to Figures 10A-10H.
 - 1f. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "NUCLEIC ACID MOLECULE ENCODING A CLASP-2 TRANSMEMBRANE PROTEIN".

Appropriate correction is required.

Claim Objections

2. Claims 1, 4-6, and 14-15 are objected to because of the following informalities:
- 2a. Claim 1, 4-6, 14-15 recite non-elected groups.
- 2b. Claim 1(c) at line 3 is missing the term “least” before the phrase “25 contiguous residues”.
- 2c. Claim 4, line 1 requires the insertion of a space keystroke between the word “claim 1” and “that”.

Appropriate correction is required.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8-17, and 32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-17, and 32 of copending Application No. 09/547,276. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the '276 application and the instant application recite an isolated Cadherin-like asymmetry protein-2 (CLASP-2) polynucleotide wherein the polynucleotide is (a) a polynucleotide that has the sequence of SEQ ID NO: 1, (b) a

polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, (c) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. Both sets of claims further recite that the polynucleotide encodes a polypeptide having the sequence of SEQ ID NO: 2 that specifically binds to a PDZ domain of DLG1. The claims recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1.

The sets of claims in the pending applications also recite an expression vector comprising the polynucleotide, a host cell, and a method for producing the polypeptide. Additionally, the claims are directed to an antisense oligonucleotide complementary to a mRNA comprising SEQ ID NO: 1 and an antisense polynucleotide less than about 200 bases in length. The claims recite a pharmaceutical composition comprising a polynucleotide and a pharmaceutically acceptable carrier. The difference between the claims of the '276 application and the instant application is the hybridization conditions recited in claim 1(b)-(d). The '276 application recites specification hybridization conditions while the instant application does not.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101 and § 112, first paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-6, 8-17, and 32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 1-6, 8-17, and 32 are directed to an isolated Cadherin-like asymmetry protein-2 (CLASP-2) polynucleotide wherein the polynucleotide is (a) a polynucleotide that has the sequence of SEQ ID NO: 1, (b) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, (c) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The claims further recite that the polynucleotide encodes a polypeptide having the sequence of SEQ ID NO: 2 that specifically binds to a PDZ domain of DLG1. The claims recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1. The claims also recite an expression vector comprising the polynucleotide, a host cell, and a method for producing the polypeptide. Additionally, the claims are directed to an antisense oligonucleotide complementary to a mRNA

comprising SEQ ID NO: 1 and an antisense polynucleotide less than about 200 bases in length.

The claims recite a pharmaceutical composition comprising a polynucleotide and a pharmaceutically acceptable carrier.

The specification asserts that the CLASP-2 polynucleotide (SEQ ID NO:1) and polypeptide (SEQ ID NO: 2) of the present invention are involved in a variety of cellular processes, particularly related to immune function, T cell activation, regulation of T cell and B cell interactions, and in the organization, establishment, and maintenance of the “immunological synapse” (including signal transduction, cytoskeletal interactions, and membrane organization) (pg 20, lines 32-33; pg 21, lines 1-5). However, the instant specification does not teach any significant characteristics of the CLASP-2 polynucleotide (SEQ ID NO: 1) or polypeptide (SEQ ID NO: 2). The specification also does not disclose any methods or working examples that indicate the polynucleotide and polypeptide of the instant invention are involved in any of the abovementioned activities. Since significant further research would be required of the skilled artisan to determine how the claimed polypeptide is involved with the above-mentioned activities, the asserted utilities are not substantial.

Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative polynucleotide (SEQ ID NO: 1):

- 1) to detect the expression of CLASP-2 in cells (pg 45, lines 31-32; pg 51-54)
- 2) in the diagnosis of a disorder or disease resulting from aberrant expression of CLASP-2 (pg 46, lines 1-19)
- 3) as hybridization probes for cDNA and genomic DNA (pg 46, lines 20-33; pg 47; pg 48, lines 1-25)

- 4) as primers for a nucleic acid amplification (pg 46, lines 20-33; pg 47; pg 48, lines 1-25)
- 5) to treat, detect, or modulate immune system disorders, hematopoietic cell disorders, allergic reactions, organ rejection or graft-versus-host disease, inflammation, infectious agents (pg 48, lines 26-34; pg 49-51)
- 6) to engineer hammerhead motif ribozyme molecules (pg 58, lines 25-34; pg 59, lines 1-4, 30-34)
- 7) for gene therapy (pg 60-64)
- 8) to construct a transgenic animal (pg 64-66)
- 9) in chromosome mapping (pg 66, lines 5-27)
- 10) to screen CLASP-2 agonists and antagonists (pg 45, lines 26-28)

Each of these shall addressed in turn.

1) *to detect the expression of CLASP-2 in cells.* This asserted utility is not specific or substantial. The specification does not disclose a specific target sequence. The specification does not disclose the cell types that express CLASP-2. Significant further experimentation would be required of the skilled artisan to identify cells and/or tissues and organs with CLASP-2. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

2) *in the diagnosis of a disorder or disease resulting from aberrant expression of CLASP-2.* This asserted utility is not specific or substantial. The specification does not disclose disorders associated with a mutated, deleted, or translocated CLASP-2 gene. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

3) as hybridization probes for cDNA and genomic DNA. This asserted utility is not substantial or specific. Hybridization probes can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) as primers for a nucleic acid amplification. This asserted utility is not substantial or specific. Primers can be designed from any polynucleotide sequence. Further, the specification does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) to treat, detect, or modulate immune system disorders, hematopoietic cell disorders, allergic reactions, organ rejection or graft-versus-host disease, inflammation, infectious agents. This asserted utility is not specific or substantial. The specification does not disclose disorders associated with a mutated, deleted, or translocated CLASP-2 gene (SEQ ID NO: 1). The specification does not disclose which disorders are associated with altered levels of the CLASP-2 gene. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) to engineer hammerhead motif ribozyme molecules. This asserted utility is not specific or substantial. Ribozymes can be designed from any DNA/RNA sequence. Additionally, the specification does not disclose a specific DNA/RNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

7) for gene therapy. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated CLASP-2 gene of SEQ ID NO: 1. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

8) to construct a transgenic animal. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated CLASP-2 gene (SEQ ID NO: 1). Significant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the gene will be “knocked in” or “knocked out” or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

9) in chromosome mapping. This asserted utility is not substantial or specific. Such assays can be performed with any polynucleotide. Further, the specification does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

10) to screen CLASP-2 agonists and antagonists. This asserted utility is not specific or substantial. Such assays can be performed with any polynucleotide. Nothing is disclosed about how the polynucleotide is affected by the compounds. Additionally, the specification discloses nothing specific or substantial for the CLASP-2 agonists and antagonists screened in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

The specification of the instant application also teaches that the CLASP-2 C-terminal 20 amino acids bind to PDZ domain-containing proteins (pg 9-10, 28-29, 120-121; Figure 9). However, relevant literature teaches that PDZ domains are among the commonest protein domains represented in sequence genomes and analysis of the human genome estimates the presence of 440 PDZ domains in at least 259 different proteins (Hung et al. J Biol Chem 277(8): 5699-5702, 2002; ¶ 1). Therefore, the asserted utility of CLASP-2 or CLASP-2 related compounds to bind to PDZ-domain containing proteins and to mediate changes in multiple protein-protein interactions involved in the function of lymphoid tissues is not specific or substantial (specification, pg 29, lines 1-6). At least 258 other PDZ-domain containing proteins could bind to CLASP-2 and/or the PDZ-domain containing proteins used in the experiments of the instant application. The specification also does not disclose any *specific* proteins that CLASP-2 may interact with in lymphoid tissue or during cell signaling. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Additionally, the utilization of CLASP-2 expression to determine T-cell activation is not a specific and substantial utility. Although Applicant indicates that CLASP-2 expression levels decrease at 1 hour, 2 hours, and 4 hours after activation (pg 123, lines 10-20; Figure 14), it cannot be determined if this decrease is a significant difference as compared to T-cells that have not been activated. If the decrease in CLASP-2 expression is not significant between the two cell types, then this utility is not specific because the skilled artisan would not be able to distinguish activated T-cells from inactivated T-cells. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted

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utility is not substantial. Applicant is encouraged to submit any evidence under 37 C.F.R. 1.132 that would indicate a significant difference between the expression of CLASP-2 in activated and inactivated T-cells.

4. Claims 1-6, 8-17, and 32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-6, 8-17, and 32 recite a CLASP-2 polynucleotide wherein the polynucleotide is a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The claims also recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1. Additionally, the claims are directed to an antisense polynucleotide less than about 200 bases in length.

The specification discloses that “the CLASP-2 variants of the invention can contain alterations in the coding regions, non-coding regions, or both” (pg 42, lines 12-13). The specification teaches that known methods of protein engineering and recombinant DNA technology can generate variants to improve or alter the characteristics of the CLASP-2

polypeptides (pg 44, lines 4-33). However, the specification does not teach any allelic variants or homologs of the CLASP-2 polynucleotide or polypeptide. The specification does not disclose (i) a polynucleotide that encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, (ii) a polynucleotide that has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1, or (iii) an antisense polynucleotide less than about 200 bases in length. The specification also does not teach a nucleic acid sequence with 90% sequence identity to the nucleotide sequence of SEQ ID NO: 1. Furthermore, the specification does not disclose any chromosomal locus for CLASP-2, which is a necessity since an allelic variant must be at the same locus. Undue experimentation is required to identify the locus and map variants to determine which ones are alleles. Additionally, the specification does not teach functional or structural characteristics of any polynucleotide variants in the context of a cell or organism.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in

underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity.

Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotide to make biologically active CLASP-2 without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

The specification does not teach the skilled artisan how to use the claimed polynucleotides encoding CLASP-2 for purposes unrelated to the asserted biological activity. For example, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the claimed polynucleotide encoding CLASP-2

could be used as a diagnostic tool. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose.

Further, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. For example, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited.

Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994,

The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, claims 13-14 and 32 are directed to an antisense polynucleotide/oligonucleotide and a pharmaceutical composition comprising a CLASP-2 polynucleotide and a pharmaceutically acceptable carrier. The specification teaches a composition comprising an isolated CLASP-2 polynucleotide consisting of the nucleic acid sequence of SEQ ID NO: 1. The specification does not teach how to use an antisense polynucleotide/oligonucleotide or CLASP-2 “pharmaceutical” composition and a “pharmaceutically acceptable carrier” without undue experimentation for the treatment of a disease in an animal. The specification lists disorders to be treated (pg 49-54), but there are no working examples directed to a particular disorder in an animal or administration of an antisense polynucleotide/oligonucleotide or CLASP-2 polynucleotide consisting of the nucleic acid sequence of SEQ ID NO: 1 to an animal for treatment. (Note, part of this issue could be overcome by deleting the terms “pharmaceutical” and “pharmaceutically acceptable” from the claims.)

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed polynucleotides encoding CLASP-2, to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, and to determine the quantity of CLASP-2 polynucleotide to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, the

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unpredictability of the effects of the CLASP-2 polynucleotide *in vivo*, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 1-6, 8-17, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, claims 1-6, 8-17, and 32 are directed a CLASP-2 polynucleotide wherein the polynucleotide is a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide having the sequence of SEQ ID NO: 2 or an allelic variant or homologue, a polynucleotide that hybridizes under stringent hybridization conditions to (a) and encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2, or (d) a polynucleotide that hybridizes under stringent hybridization conditions to (a) and has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1. The claims also recite an isolated CLASP-2 polynucleotide comprising a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1. Additionally, the claims are directed to an antisense polynucleotide less than about 200 bases in length.

The specification teaches human a CLASP-2 polynucleotide and polypeptide (SEQ ID NO: 1 and SEQ ID NO: 2, respectively). The specification also discloses that “the CLASP-2 variants of the invention can contain alterations in the coding regions, non-coding regions, or

both" (pg 42, lines 12-13). The specification teaches that known methods of protein engineering and recombinant DNA technology can generate variants to improve or alter the characteristics of the CLASP-2 polypeptides (pg 44, lines 4-33). However, the specification does not teach functional or structural characteristics of the polynucleotide variants in the context of a cell or organism. The description of one CLASP-2 polynucleotide species (SEQ ID NO: 1) and one CLASP-2 polypeptide species (SEQ ID NO: 2) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments (i) with at least 90% sequence identity to the human CLASP-2 polynucleotide comprising SEQ ID NO: 1. The description of one CLASP-2 polynucleotide species and one CLASP-2 polypeptide species is also not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments (ii) that encode a polypeptide with at least 25 contiguous residues, (iii) have at least 12 bases identical to or exactly complementary to SEQ ID NO: 1, and (iv) have antisense polynucleotide less than 200 bases in length.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is

not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated CLASP-2 polynucleotide that has the sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claim 5 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The invention appears to employ novel nucleic acid molecules (i.e., clones AVC-PD1, AVC-PD2). Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the

requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The specification does not disclose a repeatable process to obtain the nucleic acid molecules and it is not apparent if the nucleic acid molecules are readily available to the public. It is noted that Applicant has deposited the nucleic acid molecules (p. 109 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

- (a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
- (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
- (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
- (d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and
- (e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall

contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination.” The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6, 8-17, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
9. Regarding claims 2-3, the acronyms “PDZ”, “PSD95”, “DLG1”, and “neDLG” render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.
10. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., “hybridizes at wash conditions of **A** X SSC and **B** % SDS at **C**°C”), claims 1-6, 8-17, and 32 fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 8-13, 17, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pianese et al. (Genbank Accession No. X68101; 24 February 1999) in view of Sibson et al. (WO 94/01548).

Pianese et al. teach an isolated polynucleotide that encodes a polypeptide with at least 25 contiguous residues of the polypeptide of SEQ ID NO: 2 of the instant application (See sequence alignment attached to this Office Action as Appendix A; see nucleotides 365-700 of Pianese et al.; see also amino acids 864-975 of SEQ ID NO: 2 of the instant application). Pianese et al. also teach a polynucleotide that has at least 12 contiguous bases identical to or exactly complementary to SEQ ID NO: 1 of the instant application and an antisense polynucleotide less than 200 bases in length (See sequence alignment attached to this Office Action as Appendix B; see nucleotides 230-270 of Pianese et al.; see nucleotides 2466-2496 of SEQ ID NO: 1 of the instant application, for example).

Pianese et al. does not teach expression vectors, host cells, or a method of producing a polypeptide.

Sibson et al. discloses that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein (see pages 8-13).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use Pianese's DNA and the expression vector, host cell, and method of expressing and then isolating the encoded polypeptide as taught by Sibson et al. in view of Sibson's suggestion that it would be desirable to do so, as cited above.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

NCI-CGAP. Accession No. AA484945, EST database, 15 August 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
February 27, 2003

Elyabell C. Lemmeau

Appendix A

LQVLSISOLIADNGIGCTREOOSLISINNSDRLIKHSSESSDVKDILKIRPV
 LMATQMKELENDPMLVDQYSLAKSASTPMLRKTMWLSHARITYKNGDLSSEAMC
 YHVHALVAYTUTKEREADALOLOEPPVPPYSHNSCORSRSCHMFGCTARYTNTI
 DEASMEVDGQDNHDFNEDVLLMEOADGMKAERLAGLTSINSSPSMKSG
 TLETHLYDMLHRPSKVEVTRAGSDNDLQFQGFEDDEKEYLKKEPKLT
 PLSLSQRKLKYSKESSENVMIDSGSKYKNDKLSKFATVOTVTRTPDDEKLO
 ERTEFECINRHEMFPTGRRGGVVECCRTRJLHCYPRKIPM
 QHHTDINPLIVADMSKKVADLQCSAEMVMIQKLQGSVSVQVNAGAPPALAR
 AFLLDNTKYPDNKYLKEVRFQVRCQOLAVNLKEDOLEYOENKANTRE
 IFLKLSDTIPPIPGDKRTRPAPORHQDNTKHSGSRDFOILSCVLPHEPH
 VTCFVCKTURTFRANKHFCQEQEAMNGREKEPWVIFNSRFYRSWGKVHIFP*

BASE COUNT	905 a	738 c	777 g	807 t
ORIGIN				
seq_name:	gb_ro.RNTRG			
seq_documentation_block:				
DEFINITION	R. norvegicus trg mRNA.	3227 bp	mRNA	linear
ACCESSION	X68101			ROD 24-FEB-1999
VERSION	X68101.1			GI:550419
KEYWORDS	trg gene.			
SOURCE	Norway rat.			
ORGANISM	Rattus norvegicus			
MATERIAL	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Rattus.			
REFERENCE	1 (bases 1 to 3227)			
AUTHORS	Pianese,L.			
JOURNAL	Submitted (07-AUG-1992) L. Pianese, Dipartimento di Biologia, Patologia Cellulare e Molecolare, Via Pansini, Naples, ITALY			
FEATURES	location/Qualifiers			
source	1. 3227 /organism="Rattus norvegicus" /strain="Flascher" /ab_xref="Taxon:10116" /cell_line="RPE-1" /clone_id="lambdaGT" 1..2218 /gene="trg" 1..2218 /gene="trg" /codon_start=2 /protein_id="CAA48220.1" /ab_xref="GI:550420" /ab_xref="SPREMBL:Q33603" /translation="KUSRGHSPIMKVKFDVYILCFIQKHOSEMAKVNVTALSLIYKE PSFVEGRADMCAISLCYEVLCQCNNSKLISITERSQOLYFLMRNFDTGKSKFRH"			
alignment_scores:				
Quality:	2882.00	Length:	674	
Ratio:	4.827	Gaps:	6	
Percent Similarity:	88.376	Percent Identity:	86.202	
alignment-block:				
US-09-547-226-2 x RNTRG				
Align seg 1/1 to: RNTRG from: 1 to: 3227				
747 GLYHISASHNProleuMetLysValPheAspValTyroLeuCysPhele 763				
14 GGACATAGTCACATCATGAGAAATGCTTACACTGCTTA 63				
763 uGLnlySHSGInSerGluGluAlaLeuysAsnValPheThaAlaLeu 780				
64 CCAAAAGCATCACAGAACATTAAATGCTTACACTGCTTA 113				
780 rGserIeuLleUlytyspheProSerThrPhenYrguglyArgAiaASP 796				
114 GGCATTAATTAAAGTCCTCAACGCTCACGAGGGGGCAGAC 163				
797 MetCysAlaAlaAlaCysArgIleLeuLysCysAsnSerIysLe 813				
164 ATGTCGGCANCCTCTGCTAGTCAGTTCTCAAGCTAACMCRAAGCT 213				
813 uSerSerIleArgIleArgIleAsnGlnIleLeutYpheLeuMetArgA 830				
214 CAGCTCATCGGACCGAGGCCCTCCAGCTTGCTTACCTCCCTGATGAGGA 263				
830 SNAASDheAPtyrThrGlyLysIleSer-PheValaGlyThrHisLeugln 846				
314 GTCATCATCTCTCTGAGCTGCTGAGCTGGTGGATGGAGG 363				
264 ACACCTCGACTACACAGGGAGAGTCGTTTCGCGACACTACAG 313				
847 ValIleIleSerValSerGlnLeuIleAlaAspValValGlyIleGly1 863				
314 GTCATCATCTCTCTGAGCTGCTGAGCTGGTGGATGGAGG 363				
863 untrArgPhedIngInSerIleuSerIleIleAsnAspysAlaAsnserA 880				
364 ARCCASAKTCAGCAGTCCTGTCATCACACACTGCAATACCG 413				
880 SPARGEIleUlySHSthSerPhesSerSerAspValLysAspLeuIle 896				
414 AGCGGCTCATAGACACAGCTCTGCTGAGGTAGGATTGACC 463				
897 IyAqIleIleArgIleValAlaMetIleAlaMetIleAlaMetIlysgluHsgI 913				
464 AGAGGATTCGCCAACAGTCCTGATGCCAGATGAGCTGGCCAGCT 513				
913 uAsnAspProgluMetIleValAspIleuGlyTyrSerIleAlaIysSerT 930				
514 GAGGACCCAGGAGCTGGAGCTGAGTACGCCAGAGCT 563				
930 YFAlaserThProgluIeArgIleValAspSerMetAlaArg 946				
564 ACCCGACCCCTGAGCAGAGCTGGAGCAGCAGGCAAG 613				

Appendix A (cont.)

947 IleHistValIysAsnGlyAspLeuSerGluAlaAlaMetCysThrValI 963
 951 ATCCAGCTTAAATGGGACTTCAGACAGCATGCGTATGCTGCCA 663
 963 svalthrAlaIeuValAlaLglutYrleuthArglys..... 975
 964 CGTGAAGCTTGGTAGCGGATAATTCACCGGAAAGAAGCTGACCTAG 713
 975 975
 714 CACTCCAGGGGACACCTGTTCCCTACGCCATACCTCCGCCAG 763
 976 976
 764 AGGAGACCGGGAGGGCATGTCAGACAGGGTGACAGCCTTCGGGT 813
 987 IleEthIroAsnIleAspGlnLgluIaSerMetMetGluaspValGlyM 1004
 814 CATCACACCAACATGTAGAGAGCTCCATGATGAAAGATGTCGGCA 863
 1004 etGlnAspIalHsPheasnGluAspValLeuMetGluLeuLeuGluI 1020
 914 TGCCAGAGTGACTTGGAGGGCTAGCATCCCGAGCCTTCGCGAC 963
 1037 IleTerIlyleuIleProIleTerYrglySargGasp..... 1050
 964 ATCTATAACTCATCCATCATGAGAAAGGGAGCTTAGAGA 1013
 1050 1050
 1014 CTACCCACCCGTATGACACCTGCHCCCATACAGCAAAGTGACAG 1063
 1050 1050
 1064 GTCACTACTGGCCGAGCTCCGGACCTACTTCGGTSCTCT 1113
 1051 Phe.PheIusPgluaspGlyLysLglutYrleuthTerIlysg 1064
 1164 CGGACAGGGACTCTCGAGATGAGAGACGGAGAACTACACCAAG 1163
 1064 IuProIysLethrProIeSerGluIleTerGluLeuLeuIysLeu 1080
 1114 AGCCCAACTCAGCCCTGCAAGATCTCAGAGATTCAGACTCTTA 1213
 1081 TyrSerAspIysPheGlySerGluasnValIysMetIleGlnAspSerG 1087
 1214 TACTCGATAATTCTGCTTCGA 1263
 1097 YlysValAsnProIysIleAspSerIysTerIlyTerIleGlnValI 1114
 1264 CAGGTCAACCGAAGATCTGGATTCGAAGTTGCTAACATCCAGGTGA 1313
 1114 hrHisValIleProPheAspPgluIysGluIleGlnLgluIgylsThr 1130
 1314 CCCATGAGCCCGCTCTTGATGAAAGAGTACAGGAGAACACA 1363
 1147 erngGlnthrGlyIysArgGlyIysGlyIysValGluGluIcysIysArgA 1164
 1414 CACCCAGACTGGAGAGGCGGGCTGCGCTGAGGACAGGCTAACCGAC 1463
 1164 rgrIleTerIleuthAlaIleHisCysPheProIysTerValIysSerIle 1180
 GGACCATCTGACCAATACACTGCTTCCCCTTGTAAGAGGGATC 1513

1514 CCTGTCATGACCCACACTGACCTGACCCATGAGGGCCAT 1563
 1197 espglumetserLysLysValAlaLglutLeuArgGlnLeucSerSer 1214
 1564 CGTGAATGAGCAGAGCTCCACCGCTGCTCAG 1613
 1214 IagluValAspMetIleIysLeuglnIenlysLeiglnGlySerValser 1230
 1614 CTCAAGTGGACATGATCAACAGCAGCTCAACTGCAGGGCAGTGTGAC 1663
 1231 ValGlnValAlaAlaLgluIyProLeuAlaIalGlaPheLeuAspA 1247
 1664 GTCAGGTCACCTGAGCCGCTAGCATCCCGAGCCTTCCTCGATGA 1713
 1247 PTMAsnThrIysArgTerProAspAsnLysAlaLysLeuLeuLysGlu 1264
 1714 CACCAACACAAAGATCACCTGACATAGGTAACCTGCTGAGGAG 1763
 1264 alPheArgGlnPheValGluAlaCysGlyGlnAlaLeuAlaValAsnGlu 1280
 1764 TTTCAGGAATTCCTGTCAGCTGTGGCAAGCTTGGCAGTGGCAACGA 1813
 1281 ArgIleIlysgluAspGlnLgluLglutYrglyGluLgluMetIysAlas 1297
 1814 CGTCIGATTAAGAGGACCAGCTGGAGCAGACAGGAAAGATGAAAGCAA 1863
 1297 nTyrArgGluMetAlaLysGluLeuSerGluIleMetIleGluGlnIleC 1314
 1864 CTACAGGGAGATCCCGAGAGCTCTCGACATCGTCCCCAGAATT 1913
 1314 YsProIeugluGluIysTerSerValLeuProIysSerLeuHisIlehe 1330
 1914 GCCCTG.....GAGAGGACACAGCTGCTACAAATTCCCTGCACTC 1958
 1331 AsnAlaIleSerGlyTerProIysSerTerIleMetValIhsGlyMetThrSe 1347
 1959 AKGCCATCAGGGGACACCAACAGCACAGTGGTCAAGGGTGACCAAG 2008
 1347 xSerSerSerValVal 1352
 2009 TGCATCTCACTTG 2024
 m: or: AK056684

Appendix B

Appendix B (cont.)